

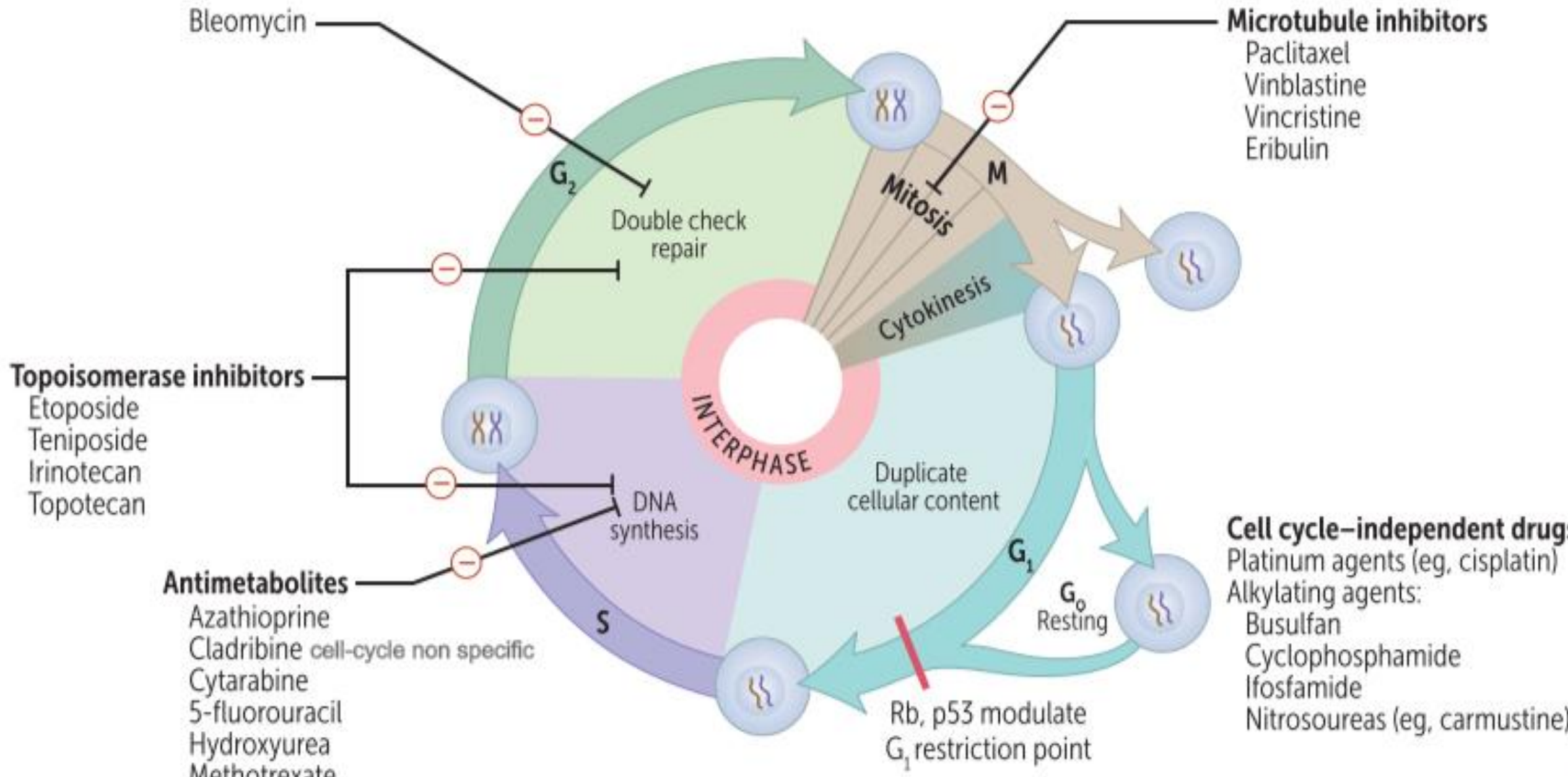
# Drug Treatment of Hematopoietic Malignancy

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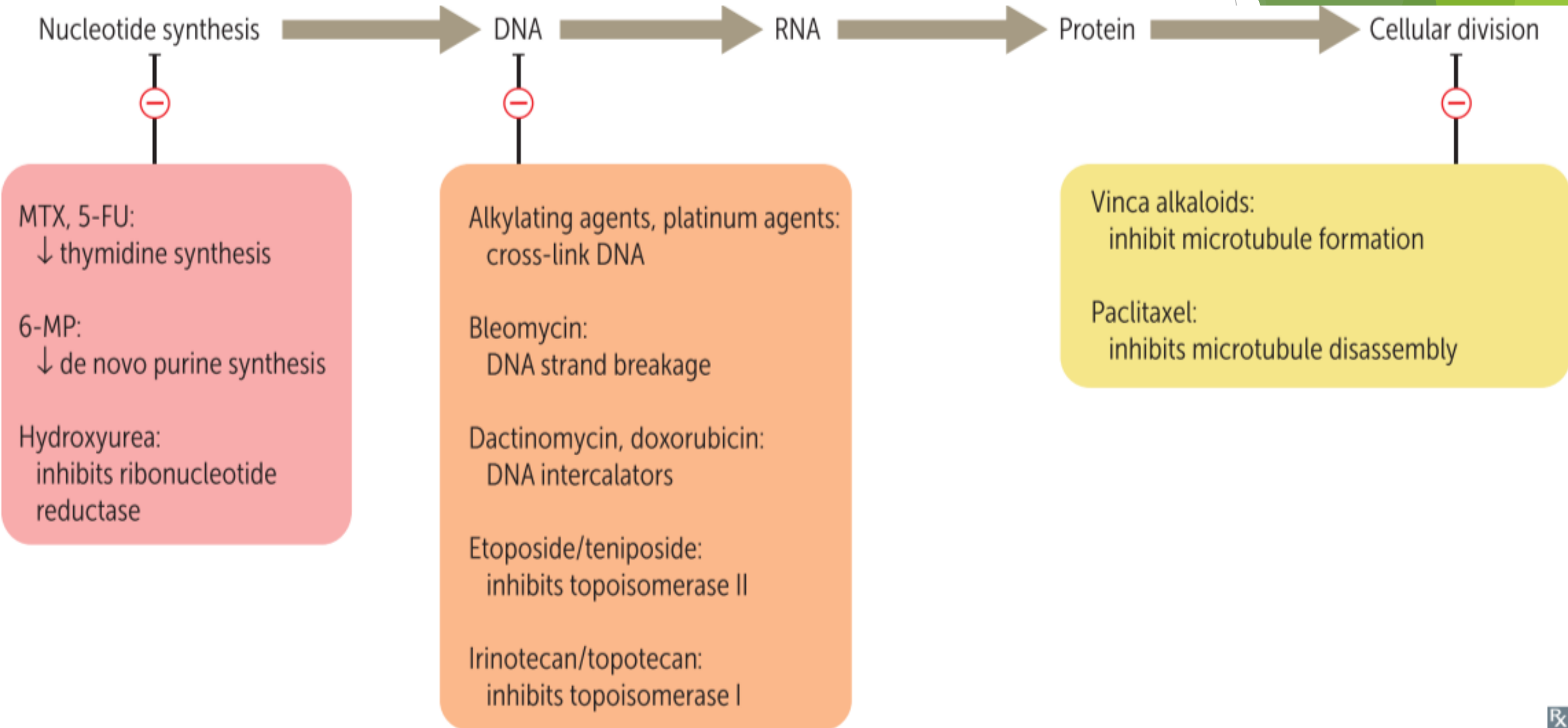
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# Cancer drugs—cell cycle



# Anticancer Drugs Targets



# Drugs used in Leukemias and Lymphomas

## Antitumor antibiotics:

- ▶ Bleomycin
- ▶ Doxorubicin, Daunorubicin

## Antimetabolites:

- ▶ Cladribine
- ▶ Cytarabine
- ▶ Methotrexate

## Alkylating agents:

- ▶ Busulfan
- ▶ Cyclophosphamide, ifosfamide
- ▶ Procarbazine

## Microtubule inhibitors:

- ▶ Vincristine
- ▶ Vinblastine

## Miscellaneous:

- ▶ Hydroxyurea
- ▶ Imatinib, dasatinib
- ▶ Rituximab

# Antitumor Antibiotics

## Bleomycin

- ▶ Induces free radical formation=> breaks in DNA strands.
- ▶ Testicular cancer, Hodgkin lymphoma
- ▶ Pulmonary fibrosis, Flagellate erythema, Minimal myelosuppression.

## Doxorubicin, Daunorubicin

- Intercalates into DNA, preventing RNA synthesis.
- Solid tumors, leukemias, lymphomas.
- Cardiotoxicity (dilated cardiomyopathy), myelosuppression, alopecia.
- Note: Dexrazoxane (iron chelating agent) is used to prevent cardiotoxicity, but it decreases the effect

# Antimetabolites

## Cladribine:

- ▶ Purine analog => multiple mechanisms (e.g. inhibition of DNA polymerase, DNA strand breaks).
- ▶ Hairy cell leukemia.
- ▶ **Myelosuppression, nephrotoxicity, and neurotoxicity.**

## Cytarabine:

- ▶ Pyrimidine analog => DNA chain termination.  
At higher concentrations, inhibits DNA Polymerase.
- ▶ Leukemias (AML), lymphomas.
- ▶ **Myelosuppression with megaloblastic anemia.**
- ▶ **CYTarabine causes panCYTopenia.**

# Antimetabolites

## Methotrexate

- ▶ Folic acid analog that competitively inhibits dihydrofolate reductase => decreases dTMP => decreases DNA synthesis.
- ▶ Cancers: leukemias (ALL), lymphomas, choriocarcinoma, sarcomas.
- ▶ Non-neoplastic: ectopic pregnancy, medical abortion (with misoprostol), rheumatoid arthritis, psoriasis, IBD, vasculitis.
- ▶ Side Effects:
  - ▶ Myelosuppression, which is reversible with leucovorin “rescue.”
  - ▶ Hepatotoxicity. Mucositis (e.g. mouth ulcers).
  - ▶ Pulmonary fibrosis.
  - ▶ Folate deficiency, which may be teratogenic (neural tube defects) without supplementation.
  - ▶ Nephrotoxicity.

# Alkylating Agents

## Busulfan

- ▶ Cross-links DNA.
- ▶ Used to ablate patient's bone marrow before bone marrow transplantation.
- ▶ Severe myelosuppression (in almost all cases), pulmonary fibrosis, hyperpigmentation.

## Procarbazine

- ▶ Cell cycle phase-nonspecific alkylating agent, mechanism not yet defined.
- ▶ Hodgkin lymphoma, brain tumors.
- ▶ Side Effects:
  - ▶ Bone marrow suppression,
  - ▶ Pulmonary toxicity,
  - ▶ Leukemia,
  - ▶ Disulfiram-like reaction.



# Alkylating Agents

## Cyclophosphamide Ifosfamide

- ▶ A nitrogen mustard
- ▶ Cross-link DNA at guanine. Require bioactivation by liver..
- ▶ Solid tumors, leukemia, lymphomas, rheumatic disease (e.g. SLE, granulomatosis with polyangiitis).
- ▶ Side Effects:
  - ▶ Myelosuppression
  - ▶ SIADH;
  - ▶ Fanconi syndrome (ifosfamide);
  - ▶ Hemorrhagic cystitis and bladder cancer, prevented with **Mesna** (sulfhydryl group of mesna binds toxic metabolites) and adequate hydration.

# Microtubule inhibitors

## ▶ Vincristine

## ▶ Vinblastine

- ▶ Vinca alkaloids bind  $\beta$ -tubulin and inhibit its polymerization into microtubules => prevent mitotic spindle formation (M-phase arrest).
- ▶ Solid tumors, leukemias, Hodgkin and non-Hodgkin lymphomas.
- ▶ Side Effects:
  - ▶ Vincristine: neurotoxicity (areflexia, peripheral neuritis), constipation (including paralytic ileus). **Crisps** the nerves.
  - ▶ Vinblastine: bone marrow suppression. **Blasts** the bone marrow.

# Miscellaneous

## ▶ Hydroxyurea

- ▶ Inhibits ribonucleotide reductase => DNA Synthesis (S-phase specific).
- ▶ Myeloproliferative disorders (e.g., CML, polycythemia vera), sickle cell (increases HbF).
- ▶ Side Effects: Severe myelosuppression.

# Tyrosine Kinase Inhibitors

## ▶ Imatinib

## ▶ Dasatinib

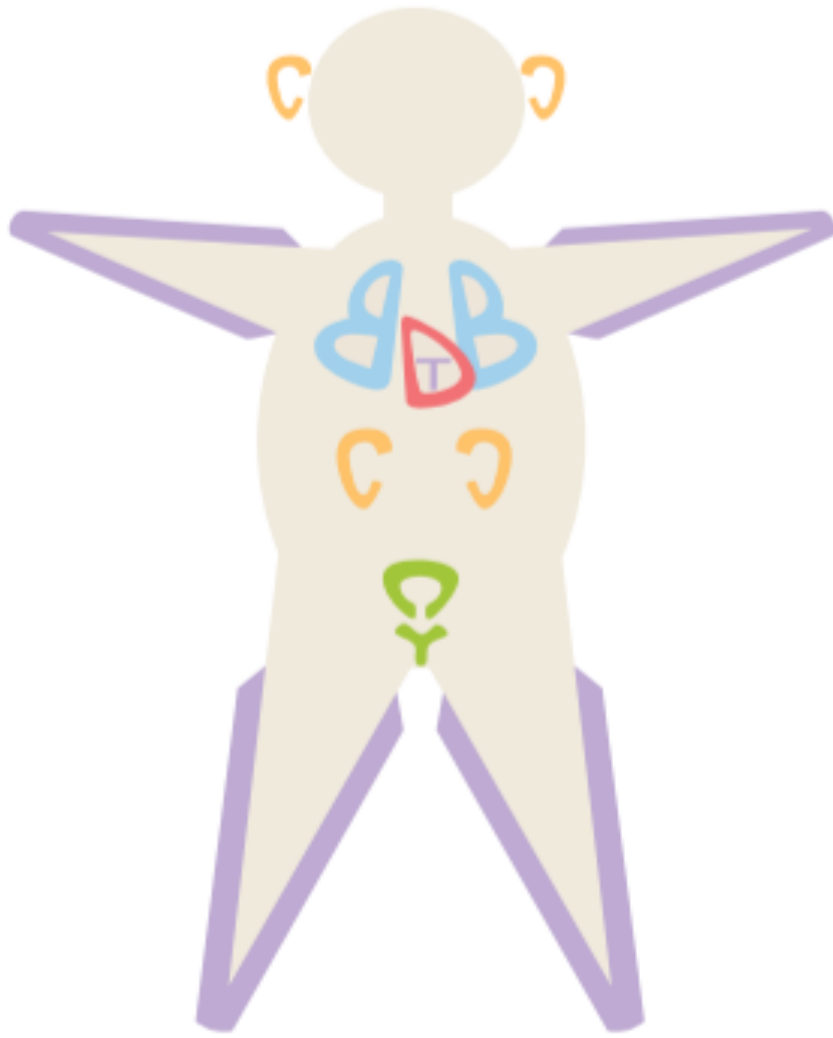
- ▶ Inhibitor of Tyrosine Kinase domains of Bcr-Abl oncoprotein(encoded by Philadelphia chromosome fusion gene in CML), PDGFR, and c-kit (common in GI stromal tumors).
- ▶ CML, GI stromal tumors (GIST).
- ▶ Safe drugs but can cause fluid retention.

# Monoclonal Antibodies

## Rituximab

- ▶ Monoclonal antibody against CD20, which is found on most B-cell neoplasms.
- ▶ Non-Hodgkin lymphoma, CLL, ITP, rheumatoid arthritis.
- ▶ **Carry the risk** of progressive multifocal leukoencephalopathy (by reactivation of JC virus) and other Opportunistic infections, also Hepatitis B reactivation
- ▶ Must screen for Hepatitis B and C before giving Rituximab

# Key chemotoxicities



Cisplatin/Carboplatin → ototoxicity

Vincristine → peripheral neuropathy

Bleomycin, Busulfan → pulmonary fibrosis

Doxorubicin → cardiotoxicity

Trastuzumab → cardiotoxicity

Cisplatin/Carboplatin → nephrotoxicity

CYclophosphamide → hemorrhagic cystitis